



RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE TABLETS OF LAMOTRIGINE USING MIXED SOLVENCY CONCEPT

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In the present investigation, newly developed solid dispersion technology that precludes the use of organic solvent and also decreases the individual concentration of hydrotropic agents, simultaneously decreasing their toxic potential; was employed for preparing dispersions of lamotrigine. Prepared solid dispersions were evaluated for flow properties, XRD, DSC, SEM and were also compressed to form tablets. Dissolution studies of prepared tablets were carried out using USP Type II Apparatus. It was concluded that the concept of mixed solvency solid dispersion is novel, safe and cost-effective technique for enhancing the bioavailability of poorly water soluble drugs by dissolving drug in non-ionized form. The tremendous enhancement in solubility of lamotrigine is clear indication of its potential to be used in future for other poorly water soluble drugs in which low bioavailability is major concern.

Key words: Mixed solvency, Lamotrigine, Eudragit, Controlled release tablet, Solid dispersion.

INTRODUCTION

Product development scientists often encounter significant difficulties in solving the problem of poor water solubility of drug candidates in the development of pharmaceutical dosage forms. Slow absorption rate results in an erratic and variable profile of drug level. A solid dispersion is a system in which the concentration of the drug is in excess of its saturation solubility at room temperature. The excess drug separates as a solid phase which is dispersed in the vehicle in crystalline or amorphous forms. Together with the permeability, the solubility behaviour of drug is key determinant of its oral bioavailability. There have always been drugs for which solubility has presented a challenge for the development of a suitable formulation for oral administration. Solid dispersion technologies are particularly promising for improving the oral absorption and

bioavailability of BCS Class II drugs. As a matter of fact, more than one third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility. Water insolubility can postpone or completely halt new drug development, and can prevent the much needed reformulation of currently marketed product (Liu, 2008).

As per the mixed solvency concept (Agrawal and Maheshwari, 2011; Chandan and Maheshwari, 2013; Maheshwari, 2009a; 2009b; 2010a; 2010b; 2014; Maheshwari *et al* 2011a; 2011b; 2011c; 2012a; 2012b; 2013; Maheshwari and Karwande, 2013; Maheshwari and Rajagopalan, 2011; 2012; Maheshwari and Shilpkar, 2012; Bhawsar *et al* 2011; Pawar *et al* 2013; Soni *et al*

2014; Sree Giri Prasad *et al* 2012; Vijayranga Vittal *et al* 2012) each and every substance (whether liquid, gas or solid) has got solubilising power.

Super critical fluid technology is based on the solubilising power of a gas, CO₂, in its liquid state. Melted PEG-4000, PEG-6000, PEG-8000 (melting point about 65-70°C) and melted urea (m.p. 132-135°C) dissolves diclofenac sodium (m.p. 283°C). This shows that melted PEGs and urea act as solvent for diclofenac sodium. Melted ibuprofen (m.p. 78°C) dissolves diclofenac sodium (m.p. 283°C), salicylic acid (m.p. 159°C) and niacinamide (m.p. 132°C) which again show that melted ibuprofen acts as solvent for diclofenac sodium, salicylic acid and niacinamide.

Mixed solvency is the increase in solubility of poorly soluble drugs by the addition of more than one solubilising agent. Use of these agents in combination may enhance the solubility of poorly soluble drugs by miraculous synergistic effect in addition to the additive effect.

Newly developed hydrotropic solid dispersion technology (Maheshwari, 2006) precludes the use of organic solvent. Salient feature of the new method is that hydrotropic agent (carrier) is water-soluble, whereas the drug is insoluble in water. However, in the presence of large amount of hydrotropic agent in water, the drug gets solubilised due to hydrotropic solubilisation phenomenon. Then water is removed by suitable evaporation technique to get a solid mass (a solid dispersion).

In absence of hydrotropic agent, water is not a solvent for poorly water soluble drugs; therefore, the proposed method is different from common solvent method and is a novel application of hydrotropic solubilisation phenomenon.

Similar to above mentioned hydrotropic solid dispersion, the present research work utilizes the mixed solvency concept for the development of a solid dispersion precluding the use of organic solvent, for making the sustained release tablets of lamotrigine. So, the objective of the present research work was to formulate the solid dispersion of lamotrigine and to develop its controlled release tablet (to reduce the side effects).

Tablet formulation comprises of solid dispersion of lamotrigine with solubility modifiers and release controlling polymers which would exhibit a similar release rate throughout the GI tract, irrespective of the pH of the environment.

MATERIALS AND METHODS

Materials

Lamotrigine was kindly donated by Torrent Pharmaceuticals Limited, Ahmedabad. Eudragit RL and Eudragit RS were purchased from Evonik Degussa, Mumbai. All the other chemicals and reagents used were of analytical grade.

Methods

Determination of solubility of lamotrigine

The solubility studies of lamotrigine were carried out in demineralised water, 0.1 N hydrochloric acid, ethanol and buffer (pH 6.8). The excess drug was added gradually to 5 millilitres of each solvent contained in 10 ml glass vials and shaken on mechanical shaker (orbital flask shaker, Khara instrument Pvt. Limited, Delhi) at room temperature for 12 h and solutions were allowed to equilibrate for 24 h, undisturbed. Then, the solutions were transferred into centrifuge tubes and centrifuged at about 2000 rotations per minute for 5 min and filtered through Whatman filter paper no 5. Aliquots of the filtrate were suitably diluted. The diluted solutions were analyzed at 306 nanometer (267 nm in case of 0.1 N hydrochloric acid) against the reagent blank.

Preparation of solid dispersions

For preparation of solid dispersion, accurately weighed polymer mixture consisting of Eudragit RS, RL and PVP K-30 were dissolved in absolute ethanol to get a clear solution. The quantity of PVP K-30 and total amount of Eudragit (Eudragit RS + Eudragit RL) was kept constant in which Eudragit RL was varied from 10% to 50%.

Accurately weighed amount of drug was dissolved in the polymer solution and stirred on a magnetic stirrer at room temperature for 4 to 6 h. After evaporation of solvent, the residue was transferred to glass plate and dried in oven at temperature of 50°C for 24 h. After complete drying, solid dispersions were crushed and triturated using a glass pestle mortar and passed through # 60 and stored in a closed glass container.

Micromeritic properties

Micromeretic properties of the solid dispersion were performed to determine bulk density, tapped density, compressibility index, Hausner ratio and angle of repose.

X-Ray diffraction studies

The powder X-ray diffraction spectra of lamo-

lamotrigine, prepared solid dispersion and the physical mixtures were obtained using RU-H₃R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International corporation, Tokyo). The sample was pressed on a graticule and pressed in such a way that the sample did not fall on keeping the graticule in vertical position. The graticule was placed in sample holder and exposed to C_Kα-radiation (40 KV, 50 MA), 2θ =5° to 50° at a scanning speed 3°/min and step size 0.04° 2θ.

Differential scanning calorimetric studies

In order to obtain the DSC thermograms of the drugs and their formulations (physical mixture and solid dispersion), a thermal analysis instrument, Pyris 6 DSC (Jade DSC) was employed. To carry out these studies, 4.3 mg of drug or formulation of drug was weighed accurately and placed in one of the matched aluminium pan. The sample pan and the reference pan both were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10°C/min with a continuous purge of nitrogen (20 ml/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 30-350°C.

Scanning electron microscopy studies

S.E.M. was used to investigate the solid state physical structure of the prepared solid dispersion. S.E.M. photographs of lamotrigine, its physical mixture with solubilizing agents and its solid dispersions were obtained using a scanning electron microscope model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV.

Preparation of Controlled release tablets incorporating lamotrigine solid dispersions

Controlled release tablets of lamotrigine was prepared (data not produced) incorporating its solid dispersion and then evaluated for in vitro dissolution studies.

In vitro release profile

The *in vitro* drug release studies of the tablets were performed using a dissolution test apparatus (USP 24 Type II, Model TDT6P) with the paddle rotating at 50 rpm in dissolution media maintained at 37±0.5°C. The dissolution media used was 0.1 N HCl / pH 6.8 buffer (1000 ml). The media was 750 ml of 0.1 N HCl for 2 h then for the remaining intervals 250 ml of trisodium phosphate buffer was added to adjust the pH to 6.8.

Ten ml aliquots of dissolution media were withdrawn at suitable time intervals and replaced with same volume of fresh dissolution media after each withdrawal. Aliquots were filtered through Whatman filter paper no. 5 and then absorbance of samples was measured at 306 nm (267 nm in case 0.1 N hydrochloric acid) against the corresponding reagent blank. The different dissolution media taken were 0.1 N HCl for first 2 h and then phosphate buffer pH 6.8.

Stability studies

The controlled release tablets of lamotrigine were kept at different storage conditions. Test samples were kept at room temperature and at 40°C. The samples were withdrawn at different time intervals and the drug contents were determined.

RESULTS AND DISCUSSION

Lamotrigine showed maximum solubility in 0.1 N HCl while least solubility in water. The results of solubility studies are summarized in **Table 1**.

Table 1. Solubility of lamotrigine in different solvents

| S. No. | Solvent | Solubility (mg/ml) | Description |
|--------|----------------------------------|--------------------|-----------------------|
| 1. | Demineralised water | 0.18 | Very slightly soluble |
| 2. | 0.1 N Hydrochloric acid (pH 1.2) | 2.75 | Very slightly soluble |
| 3. | Phosphate buffer (pH 6.8) | 0.36 | Very slightly soluble |
| 4. | Ethanol | 0.59 | Very slightly soluble |

The crystalline nature of lamotrigine was clearly demonstrated by the characteristic XRD pattern with peak appearing at 12.21, 12.25, 13.60 and 13.64 2θ values. Also the XRD patterns of drug, and PM gave sharp and intense peaks (**Figure 1, 2**). From **Figure 3**, it was observed that the number of peaks in case of solid dispersion (SD)

was less than in PM mixture. Also there was reduction in the intensities of the characteristic peaks in case of SD. This suggested that the degree of amorphousness in SD is more. The micromeritics studies indicated that SDs possessed improved flow properties and bulk density (**Table 2**).

Table 2. Summary of results of micromeritics studies of solid dispersion

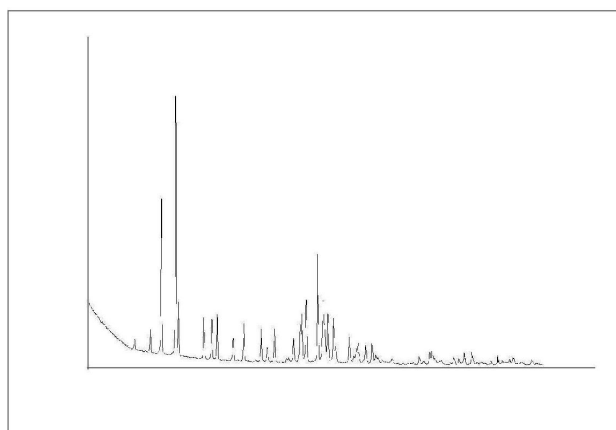
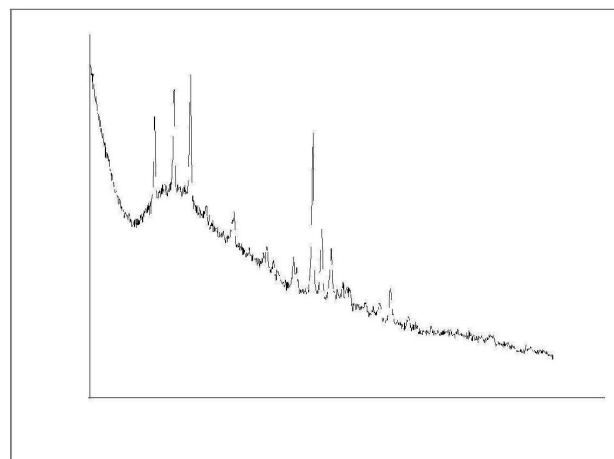
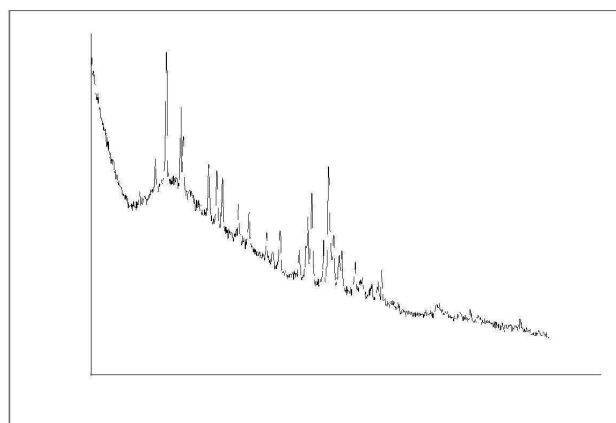
| <i>Parameter</i> | <i>Result</i> |
|-----------------------|---------------|
| Bulk density (g/cc) | 0.420 |
| Tapped density (g/cc) | 0.460 |
| Compressibility index | 10.00 |
| Hausner ratio | 1.17 |
| Angle of repose | 28.95° |

The *in vitro* dissolution studies revealed that the solid dispersion tablets were able to control the

drug release till 12 h with 85.84 to 88.05 per cent in given dissolution medium (**Table 3**).

Table 3. *In vitro* dissolution data

| Formulation | Percent cumulative drug released | | | | | | | |
|-------------------------|---|-------|-------|-------|-------|-------|-------|-------|
| | Time (h) | | | | | | | |
| | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 |
| 0.1 N HCl | 18.00 | 33.96 | 42.53 | 48.93 | 64.67 | 75.16 | 83.56 | 88.05 |
| Phosphate buffer pH 6.8 | 15.08 | 28.23 | 39.75 | 49.25 | 65.60 | 73.88 | 82.50 | 86.10 |

**Fig. 1.** X-Ray diffractogram of lamotrigine drug sample**Fig. 3.** X-Ray diffractogram of lamotrigine solid dispersion**Fig. 2.** X-Ray diffractogram of PM

DSC curve of pure drug (lamotrigine) exhibits a sharp endothermic peak at 218°C corresponding to its melting point (**Figure 4**). Solid dispersion of lamotrigine in Eudragit RS, Eudragit RL and

PVP K-30 matrix resulted in a complete suppression of the drug peak (**Figure 5**), suggesting homogeneous dissolution of the drug in the melted polymers. DSC curve for solid dispersion is nearly same as that of physical mixture, showing that there are no interactions between drug and carriers.

SEM photographs of pure lamotrigine in the **Figure 6** showed the characteristic shaped structures, indicating the crystallinity of lamotrigine. These characteristic shaped structures can also be seen along with other structures of solubilising agents in photograph of the physical mixture (**Figure 7**). But in photograph of solid dispersion, there are no distinguishable characteristic shaped structure of lamotrigine in **Figure 8**. This suggests the total miscibility within the carrier.

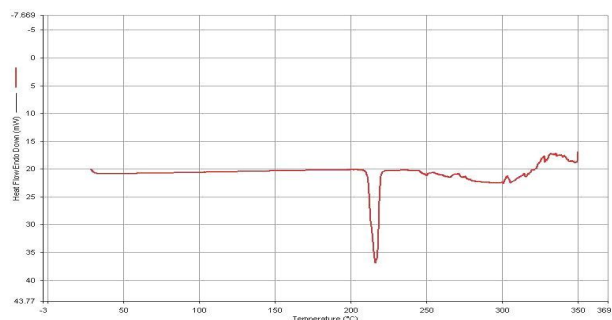


Fig. 4. DSC thermogram of lamotrigine drug sample

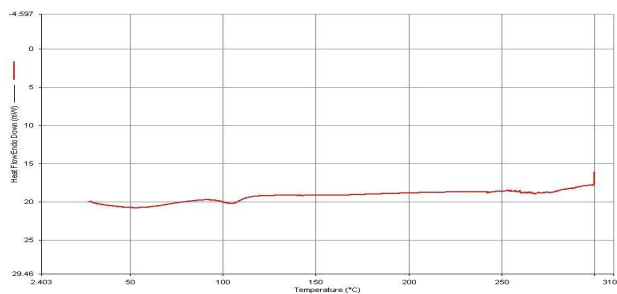


Fig. 5. DSC thermogram of lamotrigine solid dispersion

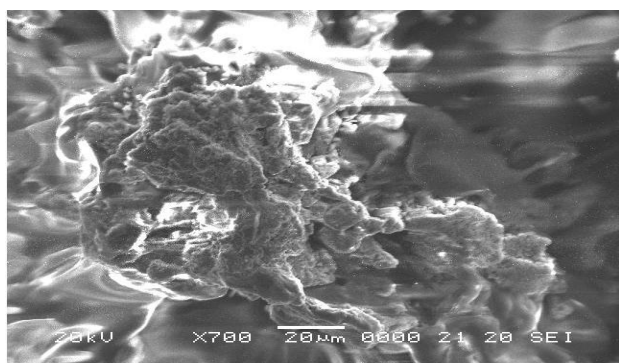


Fig. 6. SEM photograph of lamotrigine drug sample

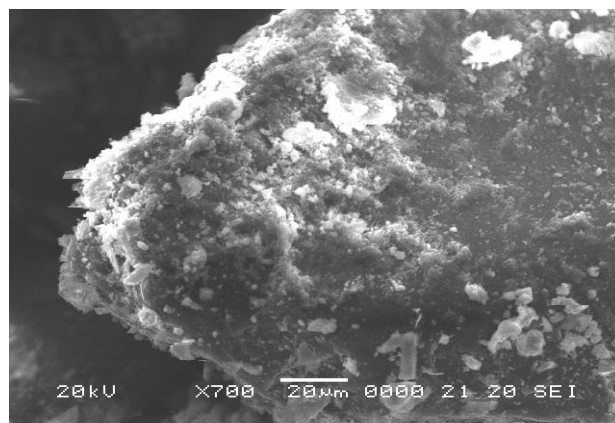


Fig. 7. SEM photograph of lamotrigine physical mixture

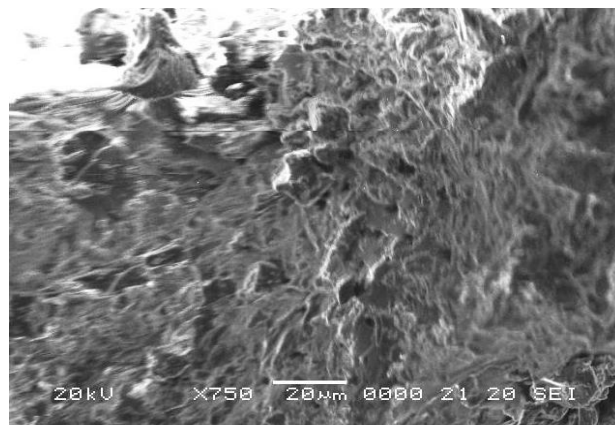


Fig. 8. SEM photograph of lamotrigine solid dispersion

The drug content was determined initially and after exposing to experimental conditions was found to be 98.75%. The controlled release tablets of lamotrigine were found to be stable at different storage conditions for the one month period (**Table 4**).

Table 4. Stability studies data

| Storage conditions | Percent drug content at various time intervals | | |
|--------------------|--|---------|---------|
| | 7 days | 15 days | 30 days |
| RT (25°C) | 98.60 | 98.47 | 98.11 |
| 40°C | 98.56 | 98.33 | 97.81 |

CONCLUSION

From the present studies, it is concluded that the mixed solvency concept can be

successfully utilized for the formulation development of the poorly water-soluble drug lamotrigine.

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